Influence of Cardiovascular and Non-Cardiovascular Comorbidities on Outcomes and Treatment Effect of Heart Rate Reduction with Ivabradine in Stable Heart Failure – (from the SHIFT trial)

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Abstract

Incidence of chronic heart failure (HF) increases with age and cardiovascular morbidity. Comorbidities increase hospitalization and mortality in HF, and non-cardiovascular comorbidities may lead to preventable hospitalizations. We studied the impact of comorbidities on mortality and morbidity in SHIFT, and investigated whether the impact of ivabradine was affected by comorbidities. We analyzed the SHIFT population, with moderate to severe HF and left ventricular dysfunction (in sinus rhythm with resting heart rate e70 bpm), according to comorbidity: chronic obstructive pulmonary disease, diabetes mellitus, anemia, stroke, impaired renal function, myocardial infarction, hypertension and peripheral artery disease. Comorbidity load was classed as: 0, 1, 2, 3, 4+ or 1–2 comorbidities or 3+ comorbidities. Comorbidities were evenly distributed between the placebo and ivabradine groups. Patients with more comorbidities were likely to be older, female, had more advanced HF; were less likely to be on beta-blockers, with an even distribution on ivabradine 2.5, 5 or 7.5 mg bid and placebo at all comorbidity loads. Number of comorbidities was related to outcomes. Cardiovascular death or HF hospitalization events significantly increased ($p<0.0001$) with comorbidity load, with the most events in patients with >3 comorbidities for both, ivabradine and placebo. There was no interaction between comorbidity load and the treatment effects of ivabradine. Hospitalization rate was lower at all comorbidity loads for ivabradine. In conclusion, cardiac and non-cardiac comorbidities significantly affect cardiovascular outcomes, particularly if there are >3 comorbidities. The effect of heart rate reduction with ivabradine is maintained at all comorbidity loads.

Key words: heart failure, heart rate, ivabradine comorbidity, comorbidity, cardiovascular death

The prevalence and incidence of chronic heart failure steadily rises with increasing age and cardiovascular morbidity. The care of heart failure patients becomes more complex due to aging-related cardiac and non-cardiac comorbidities (1), disabilities (2) and frailty (3). Moreover, treatment is progressively complicated by changes in drug pharmacokinetic and pharmacodynamics in the elderly (4), and with increased polypharmacological therapy (5). This is associated with increased economic burden for health care providers (6). Comorbidities increase hospitalization and mortality (7,8). It is unknown whether an increase in non-cardiovascular comorbidities affects the efficacy of proven medications. The SHIFT (Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial) study tested the effect of heart rate reduction with the I_f- inhibitor ivabradine in patients with systolic heart failure, left ventricular ejection fraction (LVEF) d35%, in sinus rhythm and with resting heart rate e70 bpm on maximized guidelines-directed background therapy (9). SHIFT showed a significant reduction of cardiovascular death and heart failure hospitalization with ivabradine-induced heart rate slowing (10). In the current post-hoc analysis, we studied the impact of preexisting comorbidities on mortality and morbidity in the SHIFT population and the treatment effect of ivabradine in the presence of comorbidities.

Methods

The design and the main results of SHIFT have been published previously (9-11). In brief, SHIFT was a randomized, placebo-controlled, double-blind clinical trial in patients with moderate to severe heart failure and LV dysfunction (LVEF d35%). Patients in sinus rhythm, >18 years of age with a resting heart rate e70 bpm at two consecutive visits, were randomized to either ivabradine or placebo. Ivabradine was started at 5 mg bid and adjusted when necessary to either 7.5 mg or 2.5 mg bid depending on heart rate and tolerability. All SHIFT investigators were expected to

include patients taking evidence-based medications at maximally tolerated doses for heart failure (including beta blockers). When a patient was not on a beta-blocker, or not on evidence-based target doses of beta-blocker, investigators were required to explain why and record the reasons in a dedicated case report form (CRF). The primary endpoint was a composite of cardiovascular death or hospital admissions for worsening of heart failure. All the study endpoints were adjudicated by an independent endpoint validation committee (9,10). The 8 most prominent comorbidities; chronic obstructive pulmonary disease (COPD), diabetes mellitus, anemia, stroke, impaired renal function (glomerular filtration rate $\leq$60 mL/min), myocardial infarction (MI), hypertension and peripheral artery disease (PAD) were reported in CRFs and evaluated. We studied the association of 1, 2, 3 and 4+ comorbidities on cardiovascular and non-cardiovascular outcomes and to increase sample sizes in 0 comorbidities, 1–2 comorbidities and 3 or more comorbidities.

Descriptive statistics are presented as means and standard deviation (SD) for continuous variables and as numbers and percentages for categorical variables. For baseline characteristics, the pooled placebo and ivabradine groups were divided into groups with different comorbidity loads (1, 2, 3, 4+ or 0, 1-2, 3+ comorbidities). Baseline characteristics were compared between the comorbidity groupings using ANOVA for continuous variables and a chi-square test for categorical variables. All time to event regression analyses were based on Cox proportional hazard models. Hazard ratios (HRs) and 95% confidence intervals were estimated, and p-values were calculated from the Wald statistic. Time to event curves for each treatment arm comorbidity group was estimated using the Kaplan Meier method. The effect of comorbidity load on cardiovascular outcomes was assessed, in each treatment group separately, unadjusted and adjusted for beta blocker use, New York Heart Association (NYHA) class, ventricular ejection fraction (LVEF), heart rate, ischemic or

non-ischemic pathology, age and systolic blood pressure (SBP). The treatment effect of ivabradine versus placebo was assessed in the comorbidity groups separately. We tested for evidence of a difference in the estimated treatment effect between the comorbidity groups by adding a multiplicative interaction between treatment and comorbidity group. Logistic regression analysis was used to assess each comorbidity's value as a predictor of heart rate (above/below 75 bpm). The outcomes analyzed were the primary endpoint (composite of cardiovascular death or hospital admission for worsening of heart failure) as individual components as well as death from heart failure or all-cause death, cardiovascular hospitalizations, total hospitalizations and non-cardiovascular hospitalizations. SAS (version 9.2) was used for all statistical analyses.

Results

Baseline characteristics of all patients and the impact of comorbidities on baseline characteristics are depicted in **Table 1**. Patients with higher numbers of comorbidities and in particular with 3+ comorbidities were likely to be older and more likely to be female with HF of ischemic origin. Furthermore, these patients also tended to have higher LVEF and more advanced clinical classes of heart failure. Patients with more comorbidities were less likely to be on beta-blockers, but there were similar distributions of ivabradine and placebo between the different comorbidity groups.

There was an even distribution of comorbidities between placebo and ivabradine (**Figure 1**). The most common comorbidity was history of hypertension, followed by myocardial infarction, diabetes and impaired renal function, COPD, anemia, stroke and peripheral artery disease. The majority of patients had 1, 2 or 3

comorbidities (**Figure 2A**), with 35.7% on ivabradine and 37.4% on placebo in patients with 3 or more comorbidities (**Figure 2B**). **Figure 3** shows Kaplan Meier curves from the primary endpoint according to 0, 1, 2, 3, 4+ comorbidities on ivabradine (left) and placebo (right). The numbers of cardiovascular death or heart failure hospitalizations were increased with cumulative comorbidity load for both placebo and ivabradine. We grouped patients also for 0, 1-2 and 3+ comorbidities with similar results. The event rates in each group tended to be lower with ivabradine when compared with placebo in patients with 0 or 3+ comorbidities. There was a highly significant association ($p<0.0001$) between comorbidities and cardiovascular death and first heart failure hospitalization in both groups (not shown). Hospitalization rate was lower in all groups on ivabradine. Figure 4 shows the association of 0, 1, 2, 3, 4+ comorbidities on the primary endpoint (A), heart failure hospitalization (B), heart failure mortality (C), cardiovascular mortality (D), non-cardiovascular hospitalization (E) and total hospitalization (F) on ivabradine (left) and placebo (right). Comorbidities were related to outcomes with 3 and for 4+ comorbidities had constantly higher event rates. For the majority of endpoints, eGFR was the strongest predictor. For all-cause hospitalization and non-CV hospitalization, COPD was most predictive.

In **Suppl. Table 1-4 (Supplementary material)**, similar data of the effect of comorbidities on the primary endpoint and its components as well as on heart failure mortality, all-cause mortality, cardiovascular (CV) hospitalization, total hospitalization and non-CV hospitalization are summarized. Mean heart rates at baseline did not show clinically meaningful differences significant across the different comorbidity groups (**Table 1**).

To study whether the comorbidity load had an impact on the treatment effects of ivabradine, we investigated the HRs for the primary and secondary endpoint. **Figure 5** summarizes Forest plots for the treatment effect of ivabradine versus

placebo. Again, for all mortality and morbidity outcomes, there was a significant effect or a trend in favor of the superiority of ivabradine compared with placebo. No significant heterogeneity of the treatment effect of ivabradine was observed between the comorbidity groups or different endpoints. In addition, there was no obvious effect of an increased load of comorbidities on the size of the treatment effect of ivabradine (**Table 2).** For all outcomes, as well as for all groups of different comorbidities, a trend without any evidence of heterogeneity was observed in favor of the treatment effect of ivabradine. Similar adjusted and non-adjusted patients were obtained when 0, 1, 2, 3, 4+ groups were evaluated (**Suppl. Table 5 and Suppl. Table 6**).

Discussion

This post-hoc analysis from the SHIFT study demonstrates that cardiac and non-cardiac comorbidities are associated with mortality and morbidity. In SHIFT, the most common comorbidities are hypertension, and having a history of myocardial infarction, diabetes, impaired renal function and COPD. The majority of patients in this population had 1, 2 or 3 accompanying comorbidities. The treatment effect of heart rate lowering with ivabradine was maintained for all comorbidity loads.

The presentation of chronic heart failure syndrome becomes increasingly complex due to continuous ageing, leading to a higher rate of ageing-related non-cardiovascular and cardiovascular comorbidities, hospitalization rates (7) and treatment costs (5-6). In addition to the influence of comorbidities on heart failure morbidity and mortality, in the absence of overt heart failure, comorbidities such as renal dysfunction, reduced forced expiratory volume, low hemoglobin concentration, and high white blood cell count increase the incidence of new-onset heart failure (12). As pointed out in the ESC Heart Failure Guidelines, comorbidities make the treatment of heart failure more complex as many drugs like ACE-inhibitors, ARBs and

mineralocorticoid antagonists have limitations, when renal function is impaired (13). In this contemporary, treated heart-failure population from SHIFT, similar comorbidities like coronary artery disease, COPD, renal impairment and diabetes were observed. This pattern differs from that seen in populations studied in earlier seminal studies such as SOLVD (Studies Of Left Ventricular Dysfunction)-Prevention and SOLVD-Treatment trials (8). Similar or even higher numbers of comorbidities were observed in patients in the earlier populations with preserved ejection fraction (7). The effect of e3 comorbidities on the primary outcome of SHIFT is most marked, outcomes tended to be worse in patients with no comorbidities than in patients with 1 or 2 comorbidities. There is no obvious explanation for this counter-intuitive finding. This observation may be related to the fact that relatively few patients had no comorbidities, possibly potentiating chance findings or giving more weight to presence of some specific types of comorbidities than to others. This remains an open issue. However, it is nonetheless noteworthy that the effect of ivabradine was similar in all 3 morbidity related groups, and that the difference in outcome between those with 0 versus 1-2 comorbidities was minimized after treatment with ivabradine. Another potential explanation is the fact that we selected only a limited number of comorbidities. Therefore, comorbid factors such as falls or cognitive disorders which are associated with poor outcome were not considered in our analysis.

Heart rate reduction with ivabradine reduces the composite endpoint of cardiovascular death and heart failure hospitalization at heart rates e70 bpm (10,11) and even cardiovascular death and all-cause death in patients with a heart rate e75 bpm (14). According to previous analyses from SHIFT, the treatment effect of ivabradine was maintained in patients at particularly high risk due to single comorbidities or cardiac conditions like impaired renal function (15), chronic obstructive pulmonary disease (16) and advanced age (17). In patients with

particularly low ejection fraction (<25%) and severe heart failure (NYHA III–IV), the treatment effect of ivabradine was similar when compared with milder stages (18). However, the important question remains whether treatment effects are impaired by an increased comorbidity load in heart failure patients. This report on contemporary patients on evidence-based treatment extends those of the SOLVD-Prevention and SOLVD-Treatment trial, where patients recruited in the late 1980's had a similar distribution of comorbidities (8). Since in these previous reports (8), the effect of comorbidities on outcomes is greater than those of the treatment effects, it becomes evident that a greater emphasis has to be on treatments specifically addressing comorbidities. These treatments need to be evaluated in prospective randomized trials addressing preventable hospitalizations related to non-cardiovascular comorbidities, which amount to almost half of all hospitalizations after the diagnosis of chronic heart failure (19).

Comorbidities might result in a change of the substrate and target of treatments. However, we could not observe an effect of comorbidity load on heart rate since eligibility and effectiveness for treatment with ivabradine is dependent on heart rate (11). It is important to note that no clinically relevant differences in baseline heart rates were observed in the different groups. A direct interaction with the pathophysiology of heart failure is more likely, in particular with respect to increased morbidity. Chronic pulmonary disease aggravates dyspnea (20) and has the potential to contribute to impaired LV filling (21). Renal impairment contributes to heart failure, which is related to sodium and water retention, exacerbating congestion (22), while anemia imposes an increased volume load on the heart leading to an aggravation of symptoms (23). All of these chronic conditions impose an increased oxidative stress on the cardiovascular system, which can be related to increased mortality rates. Interestingly, ivabradine can reduce oxidative stress (24), and heart rate is

associated with cognitive (25,26) and renal comorbidities in high risk patients (27), potentially providing a target of this treatment.

This is a post-hoc analysis of a study population not subject to randomization, which might lead to bias. In clinical trials, elderly individuals are underrepresented (28). Elderly patients have a higher comorbidity load (2,13) with higher levels of non-adherence to drugs (5), drug interactions and different sensitivity to the perception of heart failure symptoms (29). However, patients aged 69 years and older are sufficiently represented in SHIFT, and age has been shown not to influence treatment outcomes (17). Finally, self-reporting of comorbidities, as is usually done in trials, can lead to over- and underestimation of comorbidities. Chronic obstructive pulmonary disease is usually overestimated (by self-reporting), while cancer and renal function are underreported with reliable reporting of diabetes and heart disease (30).

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Figure legends

Figure 1

Distribution of different comorbidities according to type in patients on ivabradine or placebo. COPD (chronic obstructive pulmonary disease), diabetes mellitus, GFR (glomerular filtration rate) < 60 ml, MI (myocardial infarction), PAD (peripheral artery disease).

Figure 2

Distribution of the number of comorbidities in patients on ivabradine or placebo (A) and distribution of different comorbidity load (0, 1–2, 3+) on ivabradine or placebo (B).

Figure 3

Kaplan Meier cumulative event curves for the primary endpoint (cardiovascular death, hospitalization for heart failure according to 0, 1, 2, 3 and 4+ comorbidities on ivabradine (left) or on placebo (right).

Figure 4

Difference of the number of comorbidities (0, 1, 2, 3 and 4+ comorbidities) and hazard ratios (HR) for the primary endpoint cardiovascular death or hospitalization for heart failure (A), heart failure hospitalization (B), heart failure mortality (C), cardiovascular death (D), non-cardiovascular hospitalization (E) and total hospitalization (F) on ivabradine (left) or on placebo (right). P-values were adjusted for beta blocker use, New York Heart Association Class, left ventricular ejection

fraction, heart rate, ischemic or non-ischemic pathology, age and systolic blood pressure.

Figure 5

Effects of different comorbidity loads on hazard ratios (HR) for the primary endpoint (cardiovascular death or hospitalization for heart failure), cardiovascular (CV) and all-cause mortality, heart failure (HF) hospitalization, HF mortality, all-cause mortality, CV hospitalization, total hospitalization and CV hospitalization. P-values were adjusted for beta blocker use, New York Heart Association (NYHA) class, left ventricular ejection fraction, heart rate, ischemic or non-ischemic pathology, age and systolic blood pressure (SBP).

Table 1: Baseline characteristics

Values are presented as means±standard deviations or numbers and percentages (%).

Baseline characteristics	All patients (n=6505)	No comorbidities (n=685)	1-2 comorbidities (n=3442)	3+ comorbidities (n=2378)	P (trend)
Comorbidities, n					
COPD	730 (11.2%)	0	234 (6.8%)	496 (20.9%)	<0.001
Diabetes	1979 (30.4%)	0	587 (17.1%)	1392 (58.5%)	<0.001
Anaemia < 120	492 (7.6%)	0	123 (3.6%)	369 (15.5%)	<0.001
Stroke	523 (8.0%)	0	103 (3.0%)	420 (17.7%)	<0.001
EGFR < 60	1697 (26.1%)	0	458 (13.3%)	1239 (52.1%)	<0.001
MI	3666 (56.4%)	0	1744 (50.7%)	1922 (80.8%)	<0.001
Hypertension	4314 (66.3%)	0	2150 (62.5%)	2164 (91.0%)	<0.001
PVD	407 (6.3%)	0	50 (1.5%)	357 (15.0%)	<0.001
EGFR	74.6 (22.9)	90.4 (22.1)	78.7 (20.4)	64.1 (22.1)	<0.001
Age (years)	60.9 (11.4)	51.2 (12.7)	59.9 (10.9)	65.1 (9.4)	<0.001
Male, n	4970 (76.4%)	546 (79.7%)	2696 (78.3%)	1728 (72.7%)	<0.001
Ethnic origin, n					
White	5771 (88.7%)	505 (73.7%)	3034 (88.1%)	2232 (93.9%)	<0.001
Asian	532 (8.2%)	148 (21.6%)	278 (8.1%)	106 (4.5%)	
Other	202 (3.1%)	32 (4.7%)	130 (3.8%)	40 (1.7%)	
Current smokers, n	1118 (17.2%)	122 (17.8%)	648 (18.8%)	348 (14.6%)	<0.001
Body mass index (kg/m^2) mean (SD)	28.0 (5.1)	25.9 (5.0)	27.9 (5.0)	28.7 (5.0)	<0.001
Resting heart rate (bpm) mean (SD)	79.9 (9.6)	81.8 (11.1)	79.6 (9.4)	79.7 (9.5)	<0.001
Systolic blood pressure (mmHg), mean (SD)	121.7 (16.0)	112.5 (14.1)	121.5 (15.8)	124.6 (15.6)	<0.001
Diastolic blood pressure (mmHg), mean (SD)	75.7 (9.5)	71.8 (8.7)	76.0 (9.6)	76.3 (9.3)	<0.001
LVEF (%), mean (SD)	29.0 (5.2)	27.3 (5.7)	29.0 (5.1)	29.4 (5.0)	<0.001
NYHA Class III/IV, n	3334 (51.3%)	292 (42.7%)	1643 (47.7%)	1399 (58.9%)	<0.001
Ischemic heart failure, n	4418 (67.9%)	83 (12.1%)	2243 (65.2%)	2092 (88.0%)	<0.001
History of atrial fibrillation or flutter, n	522 (8.0%)	33 (4.8%)	249 (7.2%)	240 (10.1%)	<0.001
History of dyslipidaemia, n	1221 (18.8%)	55 (8.0%)	625 (18.2%)	541 (22.8%)	<0.001
ACE inhibitor*, n	5116 (78.6)	527 (76.9%)	2731 (79.3%)	1858 (78.1%)	0.981
ARB*, n	927 (14.3%)	82 (12.0%)	470 (13.7%)	375 (15.8%)	0.004
Diuretic*, n	5414 (83.2%)	582 (85.0%)	2771 (80.5%)	2061 (86.7%)	<0.001
Aldosterone*, n	3922 (60.3%)	514 (75.0%)	2049 (59.5%)	1359 (57.1%)	<0.001
Beta-blocker*, n	5820 (89.5%)	620 (90.5%)	3129 (90.9%)	2071 (87.1%)	<0.001
Ivabradine*, n	3241 (49.8%)	325 (47.4%)	1758 (51.1%)	1158 (48.7%)	0.682

*At randomization

Table 2: Ivabradine vs Placebo

			0 comorbidities		1-2 comorbidities		3+ comorbidties		Interaction p values	
	Ivabradine	Placebo	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	trend test	Heteroge-neity test
Primary Endpoint	68 (20.9%)	101 (28.1%)	0.74 (0.54, 1.01)	0.055	0.81 (0.70, 0.93)	0.0027	0.88 (0.76, 1.02)	0.082	0.18	0.48
CV-cause mortality	38 (11.7%)	55 (15.3%)	0.76 (0.50, 1.16)	0.20	0.94 (0.78, 1.14)	0.54	0.93 (0.77, 1.14)	0.49	0.52	0.66
HF hospitalisation	44 (13.5%)	75 (20.8%)	0.64 (0.44, 0.94)	0.022	0.72 (0.61, 0.86)	0.0002	0.81 (0.69, 0.96)	0.017	0.13	0.40
HF mortality	13 (4.0%)	19 (5.3%)	0.75 (0.37, 1.52)	0.42	0.86 (0.60, 1.24)	0.43	0.67 (0.46, 0.98)	0.038	0.54	0.69
All-cause mortality	42 (12.9%)	55 (15.3%)	0.85 (0.56, 1.27)	0.42	0.95 (0.79, 1.13)	0.53	0.90 (0.75, 1.08)	0.25	0.99	0.87
CV hospitalisation	81 (24.9%)	110 (30.6%)	0.76 (0.57, 1.01)	0.061	0.82 (0.72, 0.93)	0.0022	0.92 (0.81, 1.04)	0.18	0.11	0.33
Total hospitalisation	94 (28.9%)	122 (33.9%)	0.79 (0.60, 1.04)	0.086	0.87 (0.77, 0.97)	0.013	0.95 (0.85, 1.06)	0.37	0.13	0.35
Non-CV hospitalisation	34 (10.5%)	40 (11.1%)	0.92 (0.58, 1.46)	0.73	0.99 (0.82, 1.19)	0.90	0.89 (0.74, 1.07)	0.23	0.58	0.74

Values are presented as numbers and percentages (%)

(Adjusted for beta-blocker use, NYHA Class, LVEF, heart rate, ischaemia, age and SBP)

Suppl. Table 1 – SHIFT COMORBIDITIES ANALYSIS (unadjusted)

A – Ivabradine only

	0 (reference)	1 HR (95% CI), p-value	2 HR (95% CI), p-value	3 HR (95% CI), p-value	4+ HR (95% CI), p-value	Overall p-value
Primary Endpoint	1	0.90 (0.68, 1.20), 0.48	1.02 (0.78, 1.34), 0.89	1.24 (0.94, 1.63), 0.13	1.92 (1.44, 2.54), <0.0001	<0.0001
HF hospitalisation	1	0.93 (0.65, 1.32), 0.68	0.93 (0.66, 1.31), 0.68	1.29 (0.92, 1.82), 0.15	2.07 (1.46, 2.93), <0.0001	<0.0001
HF mortality	1	0.72 (0.36, 1.43), 0.35	0.76 (0.40, 1.44), 0.39	0.56 (0.27, 1.14), 0.11	1.71 (0.89, 3.29), 0.11	0.0012
Non-CV hospitalisation	1	0.99 (0.66, 1.49), 0.98	1.44 (1.00, 2.10), 0.052	1.46 (1.00, 2.15), 0.053	2.47 (1.67, 3.64), <0.0001	<0.0001
Total hospitalisation	1	0.99 (0.78, 1.26), 0.92	1.29 (1.03, 1.61), 0.029	1.59 (1.26, 2.00), <0.0001	2.39 (1.89, 3.04), <0.0001	<0.0001
All-cause mortality	1	0.90 (0.62, 1.30), 0.57	1.17 (0.83, 1.64), 0.37	1.09 (0.77, 1.56), 0.63	1.84 (1.29, 2.64), 0.0008	<0.0001
CV-cause mortality	1	0.89 (0.61, 1.32), 0.57	1.14 (0.80, 1.63), 0.47	1.11 (0.76, 1.62), 0.58	1.78 (1.22, 2.60), 0.0029	0.0001
CV hospitalisation	1	0.87 (0.67, 1.13), 0.30	1.12 (0.87, 1.43), 0.39	1.36 (1.06, 1.75), 0.016	2.18 (1.69, 2.83), <0.0001	<0.0001

B – Placebo only

	0 (reference)	1 HR (95% CI), p-value	2 HR (95% CI), p-value	3 HR (95% CI), p-value	4+ HR (95% CI), p-value	Overall p-value
Primary Endpoint	1	0.74 (0.57, 0.95), 0.017	0.90 (0.72, 1.14), 0.39	1.02 (0.81, 1.30), 0.84	1.52 (1.20, 1.94), 0.0007	<0.0001
HF hospitalisation	1	0.68 (0.50, 0.91), 0.0098	0.85 (0.65, 1.12), 0.25	1.02 (0.78, 1.34), 0.90	1.51 (1.14, 2.00), 0.0040	<0.0001
HF mortality	1	0.64 (0.35, 1.16), 0.14	0.65 (0.37, 1.13), 0.13	0.81 (0.46, 1.42), 0.46	1.53 (0.88, 2.66), 0.13	0.0012
Non-CV hospitalisation	1	1.14 (0.79, 1.66), 0.48	1.15 (0.80, 1.63), 0.45	1.50 (1.05, 2.14), 0.025	2.40 (1.68, 3.44), <0.0001	<0.0001
Total hospitalisation	1	0.96 (0.77, 1.19), 0.69	1.11 (0.90, 1.36), 0.33	1.33 (1.08, 1.64), 0.0065	1.97 (1.59, 2.44), <0.0001	<0.0001
All-cause mortality	1	0.89 (0.64, 1.23), 0.47	0.95 (0.70, 1.29), 0.73	1.05 (0.77, 1.45), 0.74	1.64 (1.19, 2.26), 0.0025	<0.0001
CV-cause mortality	1	0.79 (0.56, 1.10), 0.16	0.85 (0.62, 1.16), 0.31	0.88 (0.64, 1.22), 0.46	1.46 (1.05, 2.02), 0.023	<0.0001
CV hospitalisation	1	0.81 (0.64, 1.02), 0.074	1.01 (0.81, 1.25), 0.94	1.18 (0.94, 1.46), 0.15	1.74 (1.39, 2.19), <0.0001	<0.0001

Suppl. Table 2: SHIFT COMORBIDITIES ANALYSIS (adjusted for beta-blocker use, NYHA Class, LVEF, heart rate, ischaemic, age and SBP)

A – Ivabradine only

	0 (reference)	1 HR (95% CI), p-value	2 HR (95% CI), p-value	3 HR (95% CI), p-value	4+ HR (95% CI), p-value	Overall p-value
Primary Endpoint	1	0.91 (0.68, 1.23), 0.55	0.98 (0.72, 1.32), 0.88	1.16 (0.85, 1.59), 0.35	1.64 (1.18, 2.29), 0.0036	<0.0001
HF hospitalisation	1	0.96 (0.66, 1.39), 0.83	0.92 (0.63, 1.34), 0.66	1.25 (0.84, 1.84), 0.27	1.82 (1.21, 2.75), 0.0040	<0.0001
HF mortality	1	0.86 (0.42, 1.77), 0.68	0.93 (0.45, 1.92), 0.84	0.67 (0.29, 1.53), 0.34	1.84 (0.82, 4.12), 0.14	0.012
Non-CV hospitalisation	1	1.08 (0.72, 1.64), 0.70	1.64 (1.10, 2.47), 0.016	1.67 (1.09, 2.58), 0.020	2.83 (1.80, 4.44), <0.0001	<0.0001
Total hospitalisation	1	1.05 (0.81, 1.35), 0.72	1.33 (1.04, 1.71), 0.025	1.63 (1.25, 2.12), 0.0003	2.38 (1.80, 3.14), <0.0001	<0.0001
All-cause mortality	1	0.95 (0.64, 1.39), 0.78	1.20 (0.82, 1.75), 0.35	1.09 (0.73, 1.64), 0.66	1.70 (1.12, 2.60), 0.014	0.0023
CV-cause mortality	1	0.93 (0.62, 1.39), 0.73	1.15 (0.77, 1.71), 0.49	1.08 (0.71, 1.66), 0.71	1.60 (1.02, 2.50), 0.040	0.017
CV hospitalisation	1	0.88 (0.67, 1.17), 0.38	1.06 (0.81, 1.40), 0.67	1.28 (0.96, 1.71), 0.10	1.94 (1.43, 2.64), <0.0001	<0.0001

B – Placebo only

	0 (reference)	1 HR (95% CI), p-value	2 HR (95% CI), p-value	3 HR (95% CI), p-value	4+ HR (95% CI), p-value	Overall p-value
Primary Endpoint	1	0.84 (0.65, 1.09), 0.19	1.12 (0.87, 1.45), 0.39	1.22 (0.93, 1.61), 0.16	1.70 (1.27, 2.26), 0.0004	<0.0001
HF hospitalisation	1	0.83 (0.61, 1.13), 0.24	1.20 (0.89, 1.62), 0.24	1.42 (1.03, 1.95), 0.032	1.99 (1.42, 2.79), <0.0001	<0.0001
HF mortality	1	0.85 (0.46, 1.60), 0.62	1.03 (0.55, 1.94), 0.92	1.20 (0.62, 2.33), 0.59	2.13 (1.07, 4.24), 0.032	0.011
Non-CV hospitalisation	1	1.26 (0.86, 1.86), 0.23	1.32 (0.90, 1.95), 0.16	1.72 (1.14, 2.58), 0.009	2.69 (1.76, 4.11), <0.0001	<0.0001
Total hospitalisation	1	1.06 (0.84, 1.32), 0.64	1.30 (1.03, 1.63), 0.025	1.52 (1.20, 1.94), 0.0006	2.15 (1.67, 2.77), <0.0001	<0.0001
All-cause mortality	1	0.96 (0.68, 1.36), 0.82	1.04 (0.74, 1.47), 0.81	1.09 (0.75, 1.57), 0.66	1.55 (1.05, 2.27), 0.026	0.0090
CV-cause mortality	1	0.84 (0.59, 1.20), 0.34	0.92 (0.64, 1.31), 0.63	0.88 (0.60, 1.30), 0.52	1.34 (0.90, 1.99), 0.15	0.012
CV hospitalisation	1	0.87 (0.68, 1.11), 0.27	1.14 (0.89, 1.45), 0.29	1.28 (0.99, 1.66), 0.058	1.79 (1.37, 2.35), <0.0001	<0.0001

Suppl. Table 3 – Relationship between numbers of comorbidities and risk of clinical outcomes (Unadjusted results)

A – Ivabradine only (n=3241)

	0 comorbidities	1-2 comorbidities		3+ comorbidities		Overall p-value
	(reference)	HR (95% CI)	p-value	HR (95% CI)	p-value	
Primary Endpoint	1	0.97 (0.75, 1.26)	0.82	1.48 (1.14, 1.91)	<0.0001	<0.0001
CV-cause mortality	1	1.04 (0.74, 1.46)	0.83	1.35 (0.95, 1.91)	0.091	0.019
HF hospitalisation	1	0.93 (0.67, 1.28)	0.66	1.56 (1.13, 2.16)	<0.0001	<0.0001
HF mortality	1	0.74 (0.40, 1.36)	0.33	0.97 (0.52, 1.79)	0.92	0.35
All-cause mortality	1	1.06 (0.76, 1.46)	0.75	1.36 (0.98, 1.90)	0.068	0.014
CV hospitalisation	1	1.01 (0.80, 1.28)	0.93	1.65 (1.30, 2.09)	<0.0001	<0.0001
Total hospitalisation	1	1.16 (0.93, 1.44)	0.19	1.86 (1.50, 2.32)	<0.0001	<0.0001
Non-CV hospitalisation	1	1.25 (0.87, 1.80)	0.22	1.81 (1.26, 2.60)	0.0013	<0.0001

B – Placebo only (n=3264)

	0 comorbidities	1-2 comorbidities		3+ comorbidities		Overall p-value
	(reference)	HR (95% CI)	p-value	HR (95% CI)	p-value	
Primary Endpoint	1	0.83 (0.67, 1.04)	0.10	1.20 (0.97, 1.50)	0.10	<0.0001
CV-cause mortality	1	0.82 (0.61, 1.11)	0.20	1.10 (0.82, 1.48)	0.54	0.011
HF hospitalisation	1	0.78 (0.61, 1.01)	0.055	1.19 (0.93, 1.54)	0.17	<0.0001
HF mortality	1	0.64 (0.38, 1.08)	0.094	1.08 (0.65, 1.78)	0.78	0.010
All-cause mortality	1	0.92 (0.69, 1.24)	0.59	1.27 (0.95, 1.70)	0.11	0.0015
CV hospitalisation	1	0.92 (0.75, 1.14)	0.45	1.38 (1.12, 1.69)	0.0024	<0.0001
Total hospitalisation	1	1.04 (0.86, 1.27)	0.67	1.56 (1.28, 1.89)	<0.0001	<0.0001
Non-CV hospitalisation	1	1.14 (0.82, 1.60)	0.43	1.83 (1.31, 2.55)	0.0004	<0.0001

Suppl. Table 4 – Relationship between numbers of comorbidities and risk of clinical outcomes (Adjusted for beta-blocker use, NYHA Class, LVEF, heart rate, ischaemic, age and SBP)

A – Ivabradine only (n=3241)

	0 comorbidities	1-2 comorbidities		3+ comorbidities		Overall p-value
	(reference)	HR (95% CI)	p-value	HR (95% CI)	p-value	
Primary Endpoint	1	0.93 (0.70, 1.23)	0.62	1.30 (0.96, 1.76)	0.092	0.0001
CV-cause mortality	1	1.02 (0.70, 1.48)	0.93	1.20 (0.80, 1.81)	0.37	0.27
HF hospitalisation	1	0.92 (0.65, 1.31)	0.65	1.43 (0.98, 2.08)	0.060	<0.0001
HF mortality	1	0.85 (0.44, 1.66)	0.64	1.02 (0.49, 2.15)	0.95	0.65
All-cause mortality	1	1.05 (0.73, 1.49)	0.81	1.23 (0.84, 1.81)	0.28	0.22
CV hospitalisation	1	0.95 (0.74, 1.23)	0.71	1.43 (1.08, 1.89)	0.012	<0.0001
Total hospitalisation	1	1.16 (0.92, 1.47)	0.21	1.77 (1.38, 2.29)	<0.0001	<0.0001
Non-CV hospitalisation	1	1.31 (0.89, 1.92)	0.17	1.86 (1.23, 2.81)	0.0032	0.0005

B – Placebo only (n=3264)

	0 comorbidities	1-2 comorbidities		3+ comorbidities		Overall p-value
	(reference)	HR (95% CI)	p-value	HR (95% CI)	p-value	
Primary Endpoint	1	0.96 (0.76, 1.21)	0.72	1.31 (1.01, 1.70)	0.043	0.0002
CV-cause mortality	1	0.86 (0.62, 1.20)	0.38	1.02 (0.71, 1.46)	0.92	0.21
HF hospitalisation	1	0.98 (0.75, 1.30)	0.91	1.51 (1.11, 2.04)	0.0083	<0.0001
HF mortality	1	0.90 (0.51, 1.59)	0.73	1.43 (0.77, 2.67)	0.26	0.049
All-cause mortality	1	0.99 (0.72, 1.36)	0.93	1.22 (0.86, 1.73)	0.26	0.081
CV hospitalisation	1	0.98 (0.79, 1.23)	0.88	1.38 (1.08, 1.76)	0.010	<0.0001
Total hospitalisation	1	1.15 (0.93, 1.42)	0.20	1.65 (1.31, 2.08)	<0.0001	<0.0001
Non-CV hospitalisation	1	1.27 (0.89, 1.82)	0.20	1.99 (1.35, 2.94)	0.0005	<0.0001

Suppl. Table 5 – Ivabradine vs Placebo (unadjusted and adjusted for beta-blocker use, NYHA Class, LVEF, heart rate, ischaemic, age and SBP)

Interaction p-values between treatment and subgroups (0/1/2/3/4+) (adjusted, unadjusted):
Primary Endpoint (0.27, 0.31) ; HF hospitalisation (0.24, 0.30) ; HF mortality (0.78, 0.73) ; Non-CV hospitalisation (0.86, 0.96) ;
Total hospitalisation (0.09, 0.11) ; All-cause mortality (0.68, 0.73) ; CV-cause mortality (0.43, 0.47) ; CV hospitalisation (0.11, 0.11)

A: Total comorbidities – 0

			Unadjusted		Adjusted	
	Ivabradine	Placebo	HR (95% CI)	p-value	HR (95% CI)	p-value
Primary Endpoint	68 (20.9%)	101 (28.1%)	0.71 (0.52, 0.96)	0.028	0.74 (0.54, 1.01)	0.028
HF hospitalisation	44 (13.5%)	75 (20.8%)	0.62 (0.43, 0.90)	0.012	0.64 (0.44, 0.94)	0.022
HF mortality	13 (4.0%)	19 (5.3%)	0.74 (0.36, 1.49)	0.40	0.75 (0.37, 1.52)	0.42
Non-CV hospitalisation	34 (10.5%)	40 (11.1%)	0.92 (0.58, 1.45)	0.71	0.92 (0.58, 1.46)	0.73
Total hospitalisation	94 (28.9%)	122 (33.9%)	0.80 (0.61, 1.04)	0.099	0.79 (0.60, 1.04)	0.086
All-cause mortality	42 (12.9%)	55 (15.3%)	0.82 (0.55, 1.23)	0.34	0.85 (0.56, 1.27)	0.42
CV-cause mortality	38 (11.7%)	55 (15.3%)	0.74 (0.49, 1.13)	0.16	0.76 (0.50, 1.16)	0.20
CV hospitalisation	81 (24.9%)	110 (30.6%)	0.77 (0.57, 1.02)	0.068	0.76 (0.57, 1.01)	0.061

B: Total comorbidities – 1

			Unadjusted		Adjusted	
	Ivabradine	Placebo	HR (95% CI)	p-value	HR (95% CI)	p-value
Primary Endpoint	145 (19.6%)	154 (22.1%)	0.86 (0.69, 1.09)	0.21	0.90 (0.71, 1.12)	0.34
HF hospitalisation	96 (13.0%)	105 (15.1%)	0.84 (0.64, 1.11)	0.22	0.88 (0.67, 1.16)	0.36
HF mortality	22 (3.0%)	24 (3.4%)	0.85 (0.48, 1.51)	0.57	0.87 (0.49, 1.56)	0.65
Non-CV hospitalisation	78 (10.6%)	90 (12.9%)	0.78 (0.58, 1.06)	0.12	0.78 (0.58, 1.06)	0.11
Total hospitalisation	215 (29.1%)	238 (34.1%)	0.81 (0.68, 0.98)	0.028	0.83 (0.69, 1.00)	0.053
All-cause mortality	89 (12.1%)	97 (13.9%)	0.84 (0.63, 1.12)	0.24	0.86 (0.64, 1.14)	0.30
CV-cause mortality	80 (10.8%)	86 (12.3%)	0.86 (0.63, 1.16)	0.32	0.88 (0.65, 1.19)	0.40
CV hospitalisation	166 (22.5%)	185 (26.5%)	0.82 (0.66, 1.01)	0.059	0.85 (0.69, 1.05)	0.14

C: Total comorbidities – 2

			Unadjusted		Adjusted	
	Ivabradine	Placebo	HR (95% CI)	p-value	HR (95% CI)	p-value
Primary Endpoint	228 (22.4%)	266 (27.0%)	0.80 (0.67, 0.95)	0.011	0.76 (0.63, 0.90)	0.0019
HF hospitalisation	134 (13.1%)	186 (18.8%)	0.67 (0.54, 0.84)	0.0004	0.63 (0.51, 0.79)	<0.0001
HF mortality	32 (3.1%)	36 (3.6%)	0.86 (0.54, 1.39)	0.55	0.85 (0.52, 1.37)	0.50
Non-CV hospitalisation	154 (15.1%)	132 (13.4%)	1.15 (0.90, 1.45)	0.25	1.13 (0.89, 1.42)	0.31
Total hospitalisation	372 (36.5%)	383 (38.8%)	0.92 (0.80, 1.06)	0.26	0.88 (0.76, 1.02)	0.080
All-cause mortality	161 (15.8%)	153 (15.5%)	1.02 (0.82, 1.28)	0.85	1.00 (0.80, 1.25)	0.97
CV-cause mortality	142 (13.9%)	137 (13.9%)	1.01 (0.80, 1.27)	0.96	0.99 (0.78, 1.25)	0.93
CV hospitalisation	287 (28.1%)	321 (32.5%)	0.84 (0.72, 0.98)	0.032	0.80 (0.68, 0.94)	0.0071

D: Total comorbidities – 3

			Unadjusted		Adjusted	
	Ivabradine	Placebo	HR (95% CI)	p-value	HR (95% CI)	p-value
Primary Endpoint	191 (26.2%)	227 (29.9%)	0.86 (0.70, 1.04)	0.11	0.87 (0.72, 1.06)	0.16
HF hospitalisation	128 (17.6%)	167 (22.0%)	0.78 (0.62, 0.98)	0.034	0.79 (0.63, 0.99)	0.043
HF mortality	17 (2.3%)	34 (4.5%)	0.51 (0.28, 0.91)	0.022	0.52 (0.29, 0.94)	0.031
Non-CV hospitalisation	111 (15.2%)	129 (17.0%)	0.88 (0.69, 1.14)	0.34	0.87 (0.68, 1.13)	0.30
Total hospitalisation	309 (42.4%)	341 (44.9%)	0.94 (0.81, 1.10)	0.46	0.94 (0.81, 1.10)	0.44
All-cause mortality	109 (15.0%)	129 (17.0%)	0.86 (0.67, 1.11)	0.25	0.87 (0.67, 1.12)	0.29
CV-cause mortality	100 (13.7%)	108 (14.2%)	0.94 (0.72, 1.24)	0.67	0.96 (0.73, 1.26)	0.77
CV hospitalisation	240 (33.0%)	279 (36.8%)	0.88 (0.74, 1.05)	0.16	0.89 (0.75, 1.06)	0.17

E: Total comorbidities – 4

			Unadjusted		Adjusted	
	Ivabradine	Placebo	HR (95% CI)	p-value	HR (95% CI)	p-value
Primary Endpoint	161 (37.4%)	189 (41.0%)	0.89 (0.72, 1.10)	0.28	0.88 (0.72, 1.09)	0.25
HF hospitalisation	112 (26.0%)	139 (30.2%)	0.84 (0.66, 1.08)	0.18	0.83 (0.65, 1.07)	0.15
HF mortality	29 (6.7%)	38 (8.2%)	0.83 (0.51, 1.35)	0.46	0.82 (0.50, 1.34)	0.43
Non-CV hospitalisation	100 (23.3%)	117 (25.4%)	0.93 (0.72, 1.22)	0.61	0.91 (0.70, 1.19)	0.49
Total hospitalisation	241 (56.0%)	272 (59.0%)	0.97 (0.81, 1.15)	0.70	0.95 (0.80, 1.13)	0.58
All-cause mortality	102 (23.7%)	118 (25.6%)	0.94 (0.72, 1.22)	0.62	0.92 (0.71, 1.20)	0.55
CV-cause mortality	89 (20.7%)	105 (22.8%)	0.92 (0.69, 1.22)	0.55	0.90 (0.68, 1.20)	0.48
CV hospitalisation	203 (47.2%)	227 (49.2%)	0.96 (0.79, 1.16)	0.66	0.95 (0.79, 1.15)	0.62

Suppl. Table 6 – Ivabradine vs Placebo

(unadjusted and adjusted for beta-blocker use, NYHA Class, LVEF, heart rate, ischaemic, age and SBP)

A: Total comorbidities – 0

	Ivabradine	Placebo	Unadjusted		Adjusted	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Primary Endpoint	68 (20.9%)	101 (28.1%)	0.71 (0.52, 0.96)	0.028	0.74 (0.54, 1.01)	0.055
CV-cause mortality	38 (11.7%)	55 (15.3%)	0.74 (0.49, 1.13)	0.16	0.76 (0.50, 1.16)	0.20
HF hospitalisation	44 (13.5%)	75 (20.8%)	0.62 (0.43, 0.90)	0.012	0.64 (0.44, 0.94)	0.022
HF mortality	13 (4.0%)	19 (5.3%)	0.74 (0.36, 1.49)	0.40	0.75 (0.37, 1.52)	0.42
All-cause mortality	42 (12.9%)	55 (15.3%)	0.82 (0.55, 1.23)	0.34	0.85 (0.56, 1.27)	0.42
CV hospitalisation	81 (24.9%)	110 (30.6%)	0.77 (0.57, 1.02)	0.068	0.76 (0.57, 1.01)	0.061
Total hospitalisation	94 (28.9%)	122 (33.9%)	0.80 (0.61, 1.04)	0.099	0.79 (0.60, 1.04)	0.086
Non-CV hospitalisation	34 (10.5%)	40 (11.1%)	0.92 (0.58, 1.45)	0.71	0.92 (0.58, 1.46)	0.73

B: Total comorbidities – 1-2

	Ivabradine	Placebo	Unadjusted		Adjusted	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Primary Endpoint	373 (21.2%)	420 (24.9%)	0.82 (0.71, 0.94)	0.0055	0.81 (0.70, 0.93)	0.0027
CV-cause mortality	222 (12.6%)	223 (13.2%)	0.94 (0.78, 1.14)	0.54	0.94 (0.78, 1.14)	0.54
HF hospitalisation	230 (13.1%)	291 (17.3%)	0.73 (0.62, 0.87)	0.0004	0.72 (0.61, 0.86)	0.0002
HF mortality	54 (3.1%)	60 (3.6%)	0.86 (0.59, 1.24)	0.40	0.86 (0.60, 1.24)	0.43
All-cause mortality	250 (14.2%)	250 (14.8%)	0.95 (0.80, 1.13)	0.55	0.95 (0.79, 1.13)	0.53
CV hospitalisation	453 (25.8%)	506 (30.0%)	0.83 (0.73, 0.94)	0.0041	0.82 (0.72, 0.93)	0.0022
Total hospitalisation	587 (33.4%)	621 (36.9%)	0.88 (0.78, 0.98)	0.023	0.87 (0.77, 0.97)	0.013
Non-CV hospitalisation	232 (13.2%)	222 (13.2%)	0.99 (0.83, 1.19)	0.94	0.99 (0.82, 1.19)	0.90

C: Total comorbidities – 3+

	Ivabradine	Placebo	Unadjusted		Adjusted	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Primary Endpoint	352 (30.4%)	416 (34.1%)	0.87 (0.75, 1.00)	0.053	0.88 (0.76, 1.02)	0.082
CV-cause mortality	189 (16.3%)	213 (17.5%)	0.92 (0.76, 1.12)	0.43	0.93 (0.77, 1.14)	0.49
HF hospitalisation	240 (20.7%)	306 (25.1%)	0.81 (0.68, 0.95)	0.012	0.81 (0.69, 0.96)	0.017
HF mortality	46 (4.0%)	72 (5.9%)	0.67 (0.46, 0.96)	0.031	0.67 (0.46, 0.98)	0.038
All-cause mortality	211 (18.2%)	247 (20.2%)	0.89 (0.74, 1.07)	0.21	0.90 (0.75, 1.08)	0.25
CV hospitalisation	443 (38.3%)	506 (41.5%)	0.91 (0.80, 1.04)	0.16	0.92 (0.81, 1.04)	0.18
Total hospitalisation	550 (47.5%)	613 (50.2%)	0.95 (0.85, 1.07)	0.38	0.95 (0.85, 1.06)	0.37
Non-CV hospitalisation	211 (18.2%)	246 (20.2%)	0.90 (0.75, 1.08)	0.26	0.89 (0.74, 1.07)	0.23

Figure 1 – Distribution of Comorbidities

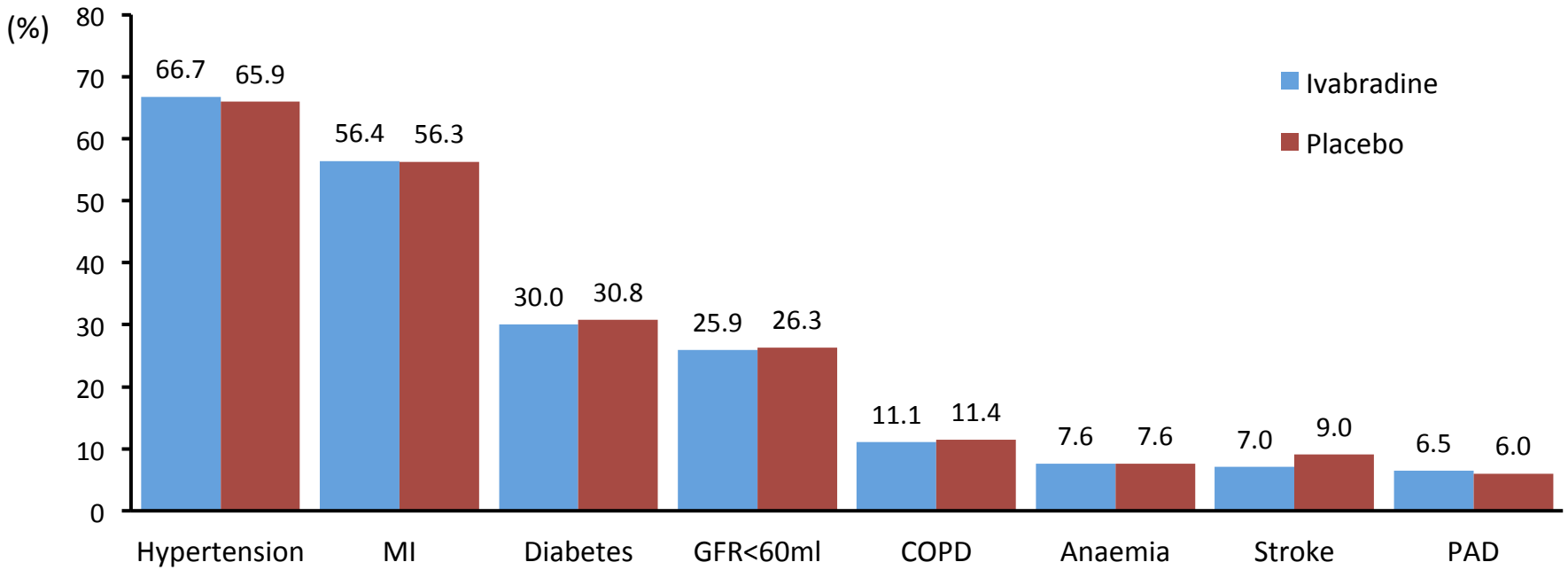

Figure 2 – Distribution of Comorbidity Numbers

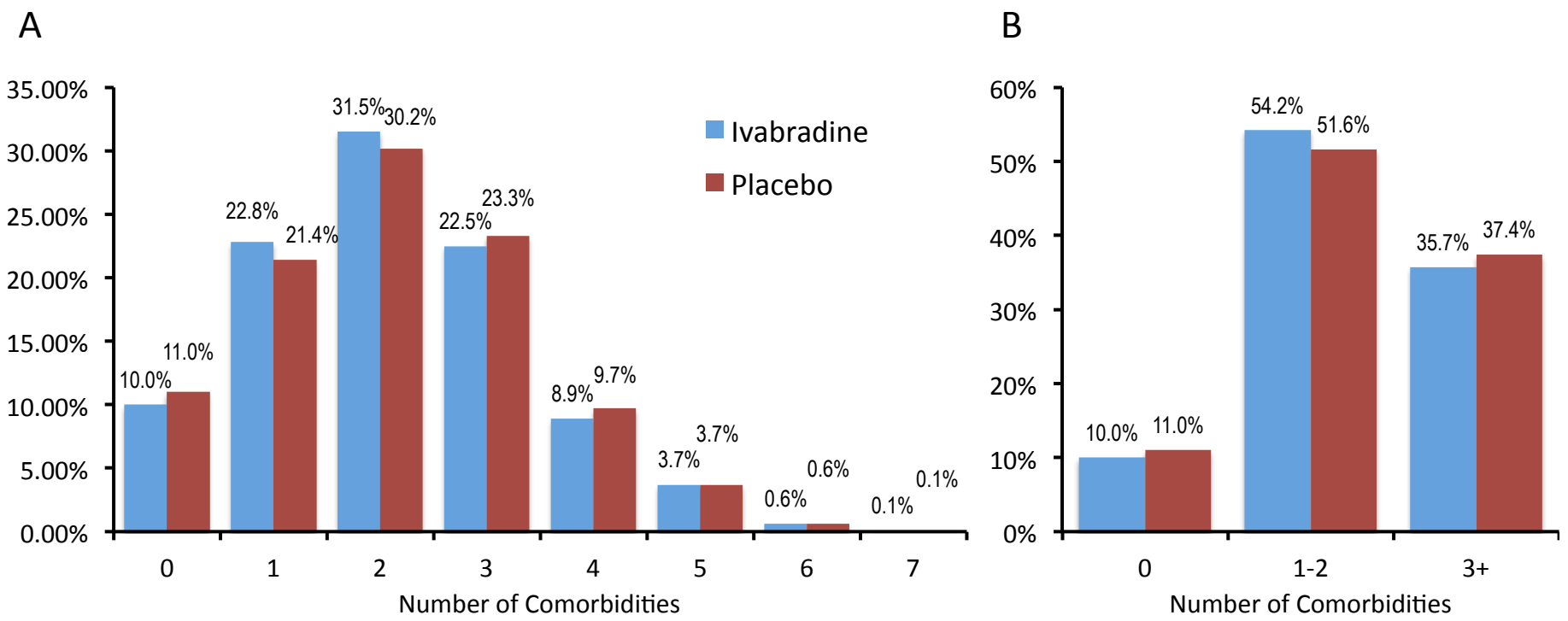

Figure 3: Primary Endpoint by Number of Comorbidities

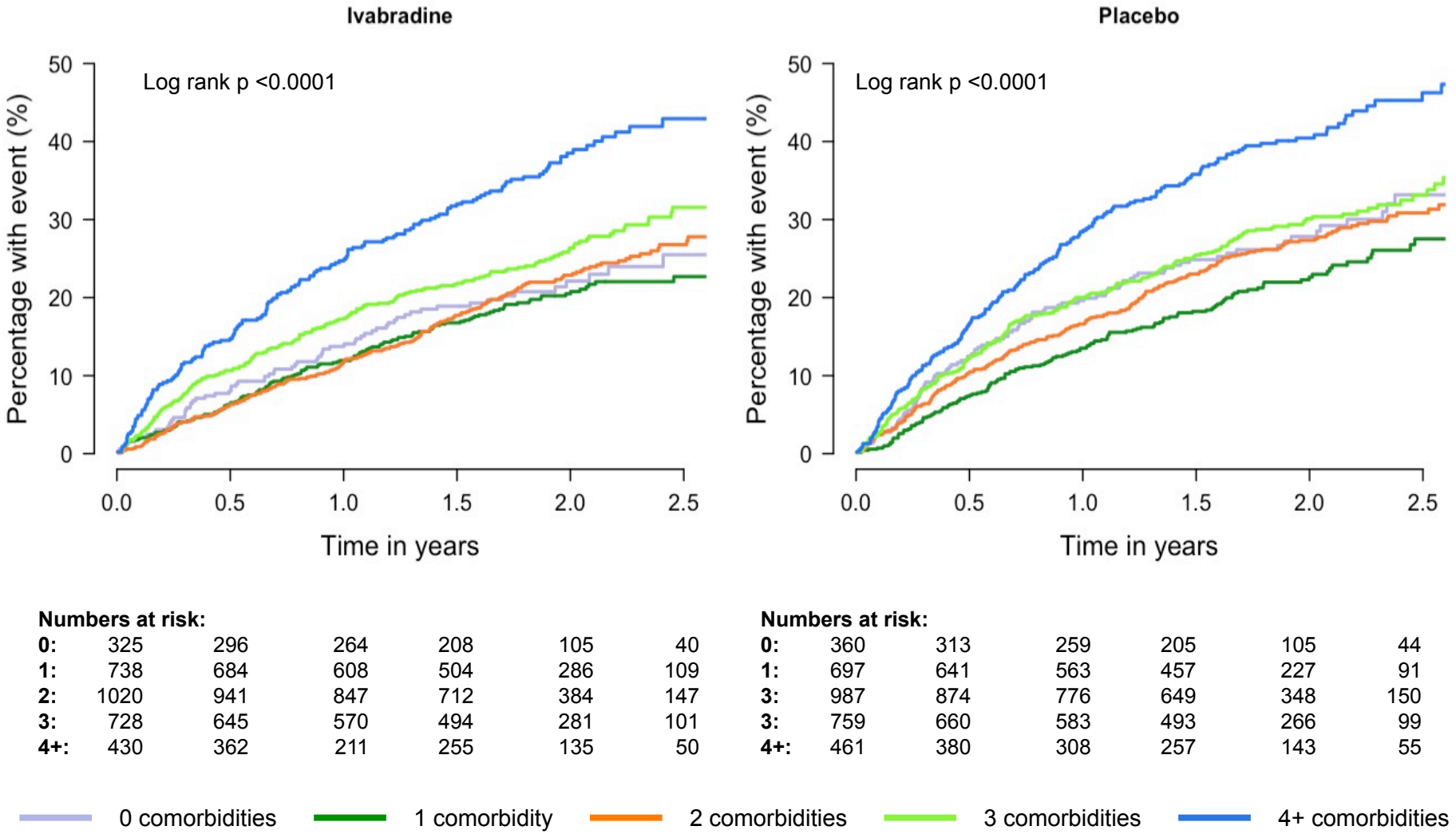

Figure 4: Adjusted HR for Number of Comorbidities relative to No Comorbidities

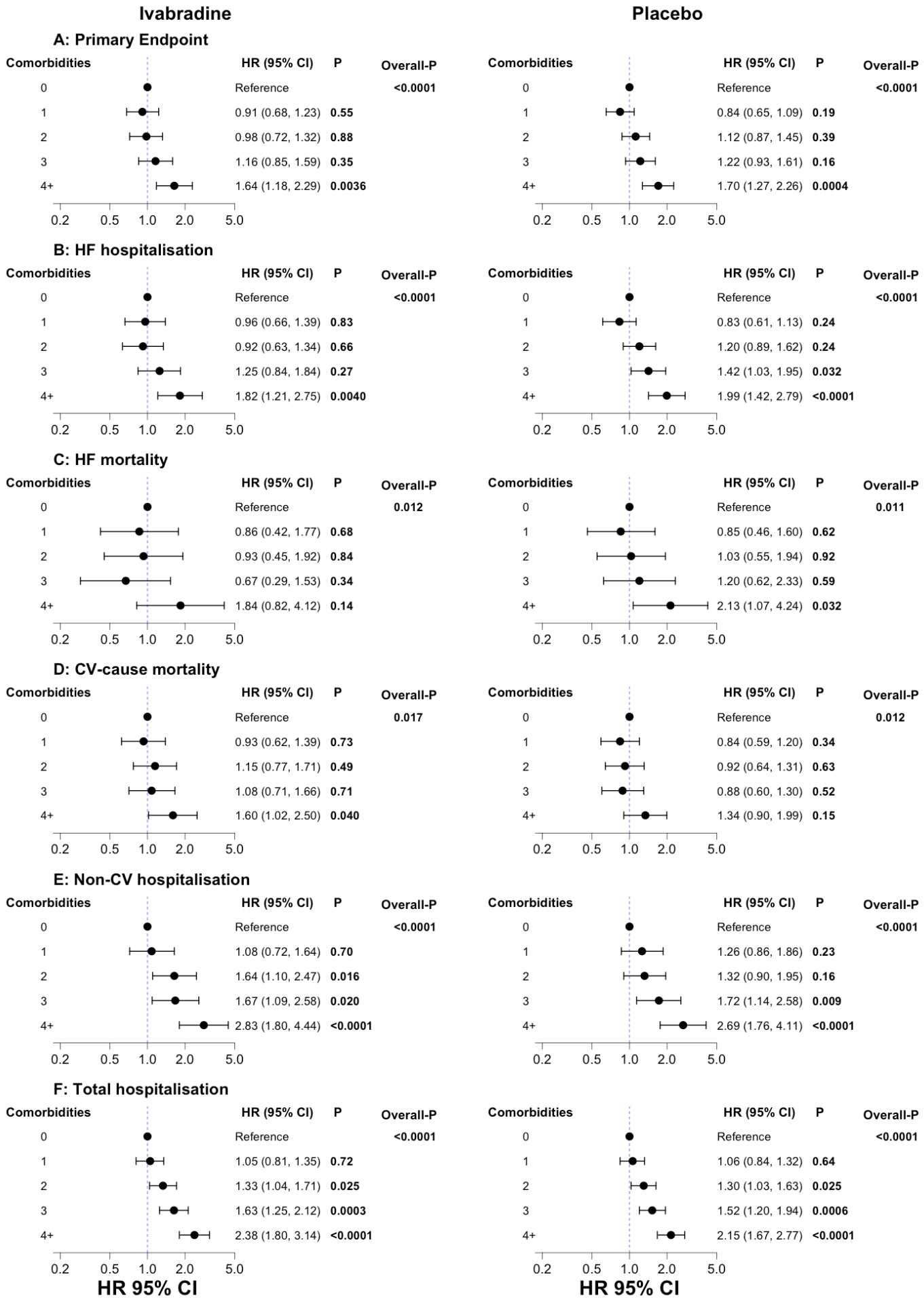

Figure 5

Ivabradine vs. Placebo